original article

Efficacy and safety of a generic rosuvastatin in a real-world setting: prospective, observational clinical study in Lebanese patients

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BACKGROUND: No published studies have assessed the efficacy and safety of rosuvastatin generics.
OBJECTIVES: Primary objective to assess the safety and efficacy of a generic rosuvastatin in reducing plasma low-density-lipoprotein cholesterol (LDL-C) in Lebanese dyslipidemic patients. Changes in high-density lipoprotein cholesterol, triglycerides and adverse effects were secondary objectives.
DESIGN: Prospective, observational, non-comparative.
SETTING: Multiple outpatient clinics in Lebanon.
PATIENTS AND METHODS: Dyslipidemic patients requiring statin therapy were followed for 2 months after prescription of a generic rosuvastatin at the physician's discretion. Efficacy and safety measurements were collected from medical records.
MAIN OUTCOME MEASURE(S): Efficacy was assessed based on the evaluation of mean and percent change in LDL-C between baseline and week 8 as well as the proportion of patients reaching target LDL-C levels. Safety was assessed based on the evaluation of the incidence of adverse events (AEs) during the study period.
RESULTS: Two months after initiation of generic rosuvastatin, LDL-C levels in the 313 eligible patients who completed the study significantly decreased from 4.3 (0.8) mmol/L (168.2 [31.3] mg/dL) at baseline to 2.7 (0.7) mmol/L (105.9 [25.5] mg/dL) (P<.001). The mean percent change in LDL-C level was highest in subjects receiving generic rosuvastatin at a dose of 40 mg/day (-47.4%), followed by 20 mg/day (-36.8%), and 10 mg/day (-31.4%); 82.5% of patients reached the target LDL-C level as set by their physician at baseline. Thirteen patients (4%) reported six AEs during treatment: abdominal pain, headache, stomach ache, insomnia, musculoskeletal pain/myalgia and nausea. No clinically significant changes in serum creatinine, serum creatine kinase, or liver function tests were reported. One patient withdrew because of an adverse event.
CONCLUSIONS: Generic rosuvastatin was efficacious and safe in reducing LDL-C levels and helping the majority of patients achieve LDL-C targets after a short treatment period.
LIMITATIONS: The observational nature, and a control group, and the relatively short duration of follow-up limit the generalizability of results. The authors received fees for study activities at patient visits from an independent clinical research organization subcontracted by the sponsor.

Hypercholesterolemia is associated with an estimated 4.4 million deaths yearly and accounts for a considerable proportion of ischemic strokes and heart disease.[1] Elevated low-density lipoprotein cholesterol (LDL-C) is established as a major modifiable risk factor in the development of atherosclerosis and cardiovascular disease (CVD).[2] Cardiovascular outcome trials for different statins have confirmed the

direct relationship between lowering LDL-C and the reduction in relative risk of cardiovascular events, validating that LDL-C is a suitable surrogate end point for statin efficacy.[3] LDL-C levels therefore continue to constitute the primary targets of therapy.[4] Epidemiologic studies also predict that every 1% reduction in LDL-C decreases the risk of major cardiovascular events by 1% to 1.5%.[5,6] Clinical evidence also points to the inverse relationship between high-density lipoprotein cholesterol (HDL-C) levels and the development of atherosclerosis.[7,8] Since coronary artery disease (CAD) is the most common type of CVD, its primary as well as secondary prevention is of great importance. Patients with the highest baseline risk are most likely to benefit.[4,9] Treatment goals depend on CVD risk stratification to identify appropriate lipid level 'targets' as recommended by the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines.[10]

Many lipid-lowering drugs have been developed, among which statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, were demonstrated in several clinical trials to be the best tolerated and most effective agents in decreasing serum cholesterol levels and reducing the risk of coronary events.[11-13] Rosuvastatin, a synthetic orally active agent, is considered the most potent statin to date.[14] It showed a dose-dependent LDL-C reduction of up to 65% and was found to be more effective than pravastatin and simvastatin in achieving LDL-C targets.[15] Another study compared rosuvastatin to the atorvastatin over 52 weeks, where the former produced greater reductions in LDL-C at the same dose in patients with primary hypercholesterolemia.[16]

In Lebanon, CVD accounts for 45% of deaths.[17] While CVD risk can be reduced by statin therapy,[7,18,19] the clinical outcome of statin therapy among Lebanese, in line with the high CVD prevalence, is not fully assessed. The Dyslipidemia International Study (DYSIS) for Jordan and Lebanon showed that more than 70% of statin-treated patients in these countries were at very high risk for cardiovascular complications. The most frequent lipid abnormality in these patients, despite chronic statin treatment, was elevated LDL-C levels. Target LDL-C levels were not reached in 67% of very high risk patients.[20]

Superstat (Resova in Saudi Arabia), a generic form of rosuvastatin manufactured by Hikma Pharmaceuticals, was launched in several countries including Saudi Arabia, Lebanon, Egypt, and Tunisia between 2010 and 2013. Superstat was determined to be bioequivalent to Crestor in a two-way, open-label, randomized, crossover study (Unpublished. Conducted by International Pharmaceutical Research Center, Amman, Jordan). The study investigated the bioequivalence of Hikma pharmaceuticals' generic rosuvastatin (20 mg rosuvastatin as calcium salt per film-coated tablet) relative to Crestor (AstraZeneca UK Limited; 20 mg rosuvastatin as calcium salt per film-coated tablet) after an oral single dose administration of 20 mg to healthy adults under fasting conditions. Thirty-two subjects completed the crossover; a one-week washout period was allowed between doses. Blood samples were collected over 72 hours and the rate and extent of absorption were analyzed based on the level of drug in human plasma, determined using liquid chromatography tandem mass spectrometry method. Both treatments were well tolerated. The two formulations (test and reference drugs) were found to have comparable 90% confidence intervals for different pharmacokinetic parameters (mean total area under the curve and maximum concentration were within the 80-125% accepted limit) and were thus considered bioequivalent.

To date, no published studies have been conducted to assess the efficacy and safety of rosuvastatin generics in a real-life setting, which is necessary to support their use for the control of hypercholesterolemia, and to reduce healthcare expenditures per patient. The objective of this study was to assess the safety and efficacy of a generic formulation of rosuvastatin in reducing plasma LDL-C in Lebanese dyslipidemic patients for both primary and secondary prevention of CVD based on total cardiovascular risk.

PATIENTS AND METHODS

This was an observational, non-comparative multicenter prospective clinical study to analyze data on the use of a generic formulation of rosuvastatin in hypercholesterolemic Lebanese adult outpatients. It included 24 cardiology, endocrinology, and general practitioner outpatient clinics; one investigator was assigned at each site. Generic rosuvastatin was prescribed at the treating physician's discretion, based on the current practice and medical indication, and independently from the recruitment into the study. Patients were followed at the clinic as per the standard practice of care for 2 months. The study protocol and informed consent were reviewed and approved by the institutional review boards of Al Rassoul Al Aazam and Hammoud Hospitals (Protocol for SPS-LBN-2014-05) before any study-related procedure took place. All patients recruited to the study gave written informed consent before any study related procedure took place or any study-related data was collected.

Data was collected from medical records and no visits or interventions outside the routine clinical practice

were requested or performed. All patients prescribed generic rosuvastatin between 3 November 2014 and 3 August 2015 were screened for eligibility. Patients were included if they were ≥18 years old, had dyslipidemia requiring statin therapy according to CVD risk factors as per the ESC/EAS 2011 guidelines for primary or secondary prevention, and provided written informed consent. Patients were excluded if they had documented statin use in the past 3 months, had any contraindication to HMG-CoA reductase inhibitors, were taking a concomitant non-statin lipid lowering agent (ezetimibe, fibrates, niacin, or omega 3 fatty acids), had conditions that might cause secondary dyslipidemia, or had a blood triglyceride (TG) level of > 4.5 mmol/L (400 mg/dL), liver enzymes (aspartate transaminase (AST) or alanine transaminase [ALT]) ≥3 upper limit normal, or serum creatine kinase (CK) > 5 upper limit normal. Efficacy was based on the evaluation of the mean and percent change in LDL-C between baseline and week 8 after the initiation of therapy. Efficacy was also based on the evaluation of mean change in TG and HDL-C between baseline and week 8, as well as the proportion of patients reaching their target LDL-C levels at week 8 as defined by the treating physician at inclusion. Safety was based on the evaluation of the incidence of adverse events (AEs) during the study period in all eligible patients. AEs could include the worsening of baseline medical conditions, the occurrence of new conditions, or a significant change in vital signs or laboratory values. Efficacy and safety measurements were collected from medical records at baseline and at week 8 after initiation, when the first assessment was expected to occur. At baseline, data collected included medical and surgical history, patient demographics, height, weight, CVD risk factors, lipid profile tests (TG, LDL-C, HDL-C, total cholesterol), and concomitant medications use. The SCORE system was used to estimate the 10-year total cardiovascular risk for each patient based on two non-modifiable (age and gender) and 3 modifiable (systolic blood pressure, total cholesterol, and smoking status) risk factors. Accordingly, patients were categorized into four CVD risk levels: very high risk, high risk, moderate risk or low risk.[4] At the final visit (month 2), data collected included lipid profile tests (TG, LDL-C, HDL-C, total cholesterol), concomitant medications use, drug prescription, and AE recording.

The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp. Released 2013). The statistical analyses consisted of descriptive statistics for parameters of interest, statistical testing of the efficacy variables, and description of safety assessments. Data was described using means and standard deviations for continuous variables and proportions for categorical variables. The change in the means for different efficacy measures between baseline and month 2 was tested using the paired t test. The testing of mean change (difference) in endpoints of interest among different dose groups was performed using ANOVA (analysis of variance). The Tukey HSD method was used for post-hoc pairwise testing. The proportion of patients who achieved their target LDL-C values was calculated and compared between different CVD risk factors groups using the chi-square test. The level of significance was set to $P \leq .05$. AEs were described as frequencies and relative frequencies. The seriousness, intensity and relatedness to study drug were also described. Mean changes in laboratory values were reported.

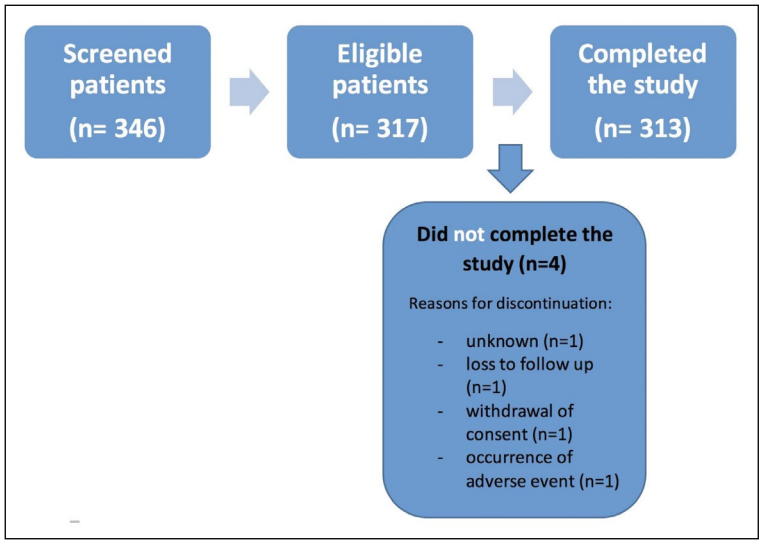

Figure 1. Patient disposition.

RESULTS

Of 346 patients screened, 313 completed the study **(Figure 1)**. The mean (SD) age of eligible patients was 55 (11.2) years and 48.6% were males **(Table 1)**. Mean body mass index was 29.2 (4.8) kg/m^2. Fifty-four patients (17.1%) had CAD, a previous stroke, or peripheral arterial disease (PAD) at baseline and 44.6% of the population had a positive family history of premature CAD. More than half of patients had hypertension and 91 patients (28.8%) had diabetes mellitus; 61.7% of the subjects were smokers, 60.9% were led a sedentary lifestyle, and 46.1% were obese. Based on the SCORE system for CVD risk estimation, almost half of the study subjects were in the very high-risk group and only 6.6% were in the low-risk group.

Table 1. Descriptive statistics of baseline characteristics, cardiovascular disease, and cardiovascular risk factors.

Characteristic	Statistic	Value
Age (years) (n=287)	Mean (SD)	55 (11.2)
	Min – Max	23 – 93
Sex (n=315)	Male n (%)	153 (48.6)
	Female n (%)	162 (51.4)
Body mass index* (kg/m^2) (n=301)	Mean (SD)	29.2 (4.8)
	Min – Max	20.2 – 46.6
Systolic blood pressure (mmHg) (n=292)	Mean (SD)	137.8 (19.4)
	Min – Max	100 – 210
Diastolic blood pressure (mmHg) (n=292)	Mean (SD)	83.1 (9.8)
	Min – Max	60 – 120
Known CVD (other than hypertension) (n=315)	No	261 (82.9)
	Yes	54 (17.1)
If yes (n=51)	CAD	41 (75.9)
	Stroke	9 (16.7)
	PAD	1 (1.9)
Positive family history of premature CAD (n=307)	No	170 (55.4)
	Yes	137 (44.6)
Hypertension (n=316)	No	144 (45.6)
	Yes	172 (54.4)
Chronic kidney disease (n=288)	No	281 (97.6)
	Yes	7 (2.4)
Diabetes mellitus (n=316)	No	225 (71.2)
	Yes	91 (28.8)
If yes (n=91)	T2DM	87 (95.6)
Familial hypercholesterolemia (n=303)	No	222 (73.3)
	Yes	81 (26.7)
Current smoking (n=316)	No	121 (38.3)
	Yes	195 (61.7)
Obesity (BMI>30 kg/m^2) (n=304)	No	164 (53.9)
	Yes	140 (46.1)
Sedentary life style (n=312)	No	122 (39.1)
	Yes	190 (60.9)

Table 1 cont. Descriptive statistics of baseline characteristics, cardiovascular disease, and cardiovascular risk factors.

Characteristic	Statistic	Value
CVD risk†		
Very high risk	144 (49.7)	
High risk	68 (23.4)	
Moderate risk	59 (20.3)	
Low risk	19 (6.6)	

Data are number (percentage) unless indicated otherwise.
*Body mass index= weight (kg)/height (m^2). †ECS/EAS Guidelines[4]. CVD: cardiovascular disease, CAD: coronary artery disease, PAD: peripheral arterial disease, T2DM: type 2 diabetes mellitus.

Generic rosuvastatin was administered at a dose of 10 mg/day in 116 patients (36.6%), 20 mg/day in 196 patients (61.8%) and 40 mg/day in 5 patients (1.6%). By the end of the study (at month 2 after treatment initiation), 1 subject (0.3%) was on a dose of 5 mg/day, 113 subjects (35.6%) were on a dose of 10 mg/day, 199 (62.8%) were on a dose of 20 mg/day and 4 (1.3%) were on a dose of 40 mg/day.

LDL-C levels significantly decreased from 4.3 (0.8) mmol/L (168.2 [31.3] mg/dL) at baseline to 2.7 (0.7) mmol/L (105.9 [25.5] mg/dL) after two months **(Table 2)** (*P*<.001).The mean change in LDL-C showed a statistically significant difference between the 3 dose-groups; pairwise post-hoc analysis for mean LDL-C change showed significant differences between the 10 and 20 mg dose groups (*P*<.001), 10 and 40 mg dose groups (*P*=.021), but not between the 20 and 40 mg dose groups (*P*=.425). The mean percent change in LDL-C was -35.0% (21.1%) in the total population. There was a statistically significant difference in the mean percent change in LDL-C level between the three dose groups (*P*=.039). The mean percent change was highest in subjects receiving rosuvastatin at a dose of 40 mg/day (-47.4%), followed by 20 mg/day (-36.8%), and 10 mg/day (-31.4%).

At the second month, 260 patients (82.5%) reached their target LDL-C level as set by their physician at baseline **(Table 3)**. Among these patients, LDL-C levels significantly decreased from 4.3 (0.8) mmol/L (165.9 [32.1] mg/dL) at baseline to 2.6 (0.6) mmol/L (101.8 [24.5] mg/dL) at month 2. Mean change was -1.7 (0.9) mmol/L (-64 [35.5] mg/dL) and percent reduction was 32.6% (22.5%). There was no statistically significant difference in the proportion of patients reaching their target LDL-C level between the three dose groups. Reasons for non-achievement of target LDL-C levels included non-compliance with lifestyle modifications, need for a higher rosuvastatin dose, and primarily the need for a longer treatment period.

Mean TG levels significantly decreased from 2.1

Table 2. Mean and percent change in LDL-C levels between baseline and Month 2 among different dose groups.

	Statistic	Total		10 mg/day		20 mg/day		40 mg/day		*P* value
		Base-line	Month 2	Base-line	Month 2	Base-line	Month 2	Base-line	Month 2	
LDL-C (mmol/L)	**Mean (SD)**	4.3 (0.8)	2.7 (0.7)	4.1 (0.5)	2.8 (0.5)	4.5 (0.9)	2.7 (0.7)	5.1 (1.0)	2.7 (1.1)	
	Min, Max	1.6, 7.5	1.2, 5.2	2.0, 5.4	1.6 , 4.4	1.6 , 7.5	1.2 , 5.2	3.4 , 6.1	1.6, 4.1	
	***P* value**	**<.001**		**<.001**		**<.001**		**.003**		
Change in LDL-C (mmol/L)*	**Mean (SD)**	-1.6 (0.9)		-1.3 (0.6)		-1.8 (1.0)		-2.4 (0.8)		<.001
	Min, Max	-4.8, 2.3		-2.6, 0.1		-4.8, 2.3		-3.3, -1.3		
Percent change in LDL-C	**Mean (SD)**	-35.0 (21.1)		-31.4 (12.6)		-36.8 (24.7)		-47.4 (14.9)		.039
	Min, Max	-76.3, 101.5		-62.5, 2.6		-76.3, 101.5		-6.8, -24.8		

*Pairwise comparisons: 10 mg and 20 mg dose groups (*P*<.001), 10 mg and 40 mg dose groups (*P*=.019), 20 mg and 40 mg dose groups (*P*=.305). Statistical analysis by one-way ANOVA (for change in LDL-C: F statistic=13.554, *P*<.001; for percent change in LDL-C: F statistic=3.260, *P*=.040)

Table 3. Comparison of the proportion of patients meeting target LDL-C levels between different dose groups and reasons for non-achievement of target LDL-C levels.

		10 mg/day	20 mg/day	40 mg/day	Total	*P* value
LDL-C target achieved (n=315)		n=115	n=195	n=5	n=315	.465
	No	24 (20.9%)	30 (15.4%)	1 (20.0%)	55 (17.5%)	
	Yes	91 (79.1%)	165 (84.6%)	4 (80.0%)	260 (82.5%)	
Reason for not achieving LDL-C target (n=55)	Non – compliance with life style modification	6 (25.0%)	13 (43.3%)	1 (100%)	20 (36.4%)	.900
	Higher dose needed	9 (37.4%)	7 (23.3%)	0 (0.0%)	16 (29.1 %)	.557
	Extra time needed	15 (62.5%)	21 (70.0%)	1 (100.0%)	37 (67.3%)	.270
	Other	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	.562
	Missing	1 (4.2%)	5 (16.7%)	0 (0.0%)	6 (10.9%)	

Data are number (percentage).

(0.7) mmol/L (189.4 [59.3] mg/dL) at baseline to 1.8 (0.5) mmol/L (158.7 [46.4] mg/dL) after two months (*P*<.001); the mean percent change was -13.2% (20.9%) **(Table 4)**. Total HDL-C levels significantly increased from 1.0 (0.3) mmol/L (40.5 [10.1] mg/dL) at baseline to 1.1 (0.3) mmol/L (43.0 [9.7] mg/dL) after two months (*P*<.001); the mean percent change was 8.2% (18.1%).

Thirteen patients (4.1%) reported 6 AEs: abdominal pain, headache, stomach ache, insomnia, musculoskeletal pain/myalgia, and nausea **(Table 5)**. Only one patient discontinued the drug secondary to headache and insomnia. A statistically significant difference was found in mean AST, ALT, serum creatinine, and serum creatine kinase levels between baseline and month 2 **(Table 6)**. However, mean levels remained within the acceptable range. There was no statistically significant difference in the mean change in liver function tests, serum creatinine, and serum creatinine kinase between different dose groups.

Table 4. Mean and percent changes in triglycerides and HDL-C levels between baseline and Month 2 after the initiation of generic rosuvastatin.

	Statistic	Triglycerides		HDL-C	
		Baseline	Month 2	Baseline	Month 2
Levels (mmol/L)	n	317	314	317	312
	Mean (SD)	2.1 (0.7)	1.8 (0.5)	1.0 (0.3)	1.1 (0.3)
	Min, Max	0.7, 4.4	0.7, 5.4	0.6, 2.4	0.6, 2.2
	P value	<.001		<.001	
Change in levels (mmol/L)	n	314		312	
	Mean (SD)	-0.4 (0.5)		0.1 (0.2)	
	Min, Max	-2.4, 1.5		-1.5, 1.0	
Change in levels (%)	Mean (SD)	-13.2 (20.9)		8.2 (18.1)	
	Min, Max	-66.5, 131.1		-63.0, 108.1	

Table 5. Description of adverse events.

Adverse event	n (%)	Serious		Intensity		Relatedness to study: treatment		Action taken		Outcome of event	
Abdominal pain	4 (1.3)	No	4 (100.0)	Mild	3 (75.0)	Likely	4 (100.0)	None	4 (100.0)	Recovered	3 (75.0)
				Moderate	1 (25.0)			Recovering	1 (25.0)		
Headache	4 (1.3)	No	4 (100.0)	Mild	4 (100.0)	Likely	3 (75.0)	None	3 (75.0)	Recovered	4 (100.0)
						Unlikely	1 (25.0)	Discontinuation	1 (25.0)		
Insomnia	1 (0.3)	No	1 (100.0)	Moderate	1 (100.0)	Likely	1 (100.0)	Discontinuation	1 (100.0)	Not recovered	1 (100.0)
Musculoskeletal pain/ myalgia	10 (3.2)	No	10 (100.0)	Mild	8 (80.0)	Likely	8 (80.0)	None	9 (90.0)	Recovered	5 (50.0)
				Moderate	2 (20.0)	Unlikely	2 (20.0)	Dose reduction	1 (10.0)	Recovering	2 (20.0)
										Not recovered	3 (30.0)
Nausea	1 (0.3)	No	1 (100.0)	Mild	1 (100.0)	Likely	1 (100.0)	None	1 (100.0)	Recovered	1(100.0)
Stomach ache	1 (0.3)	No	1 (100.0)	Mild	1 (100.0)	Likely	1 (100.0)	None	1 (100.0)	Recovering	1 (100.0)

Data are number (percentage).

DISCUSSION

Managing patients with dyslipidemia includes lifestyle changes (diet and exercise) as well as drug therapy. In this context, statins are recognized as essential agents for the reduction of CAD risk. Accordingly, this was an observational study assessing the efficacy and safety of a generic formulation of rosuvastatin, in a total of 317 Lebanese hypercholesterolemic patients in routine clinical settings. The study population was heterogeneous and included patients with hypertension (54.4%) and diabetes (28.8%), and patients who were in general at high/very high risk of developing CVD (73.1%).

The mean percent change in LDL-C level was -35% after 2 months of treatment, which is comparable to that reported in other observational studies.[21] Our efficacy results, however, differ from those of some earlier randomized controlled trials (RCTs) using the original rosuvastatin (Crestor).[15,22,23] In one study, the reported mean percent change from baseline to week 6 was -50.5%, -57.0%, and -62.6% for the 10-, 20-, and 40-mg dose groups, respectively. This difference can be explained by several factors. Patients in RCTs designed to prove efficacy had higher baseline cholesterol levels (4.1-5.7 mmol/L (160-220 mg/dL)), were healthier (no CVD, diabetes, or obesity), and represented a homogenous group in controlled conditions.[22]

Although no studies have been performed on rosuvastatin generics, several studies on other statin generics have found comparable efficacy and safety profiles between generic and innovator statins with short- or long-term use,[24,25] even in high-risk populations.[26] One Swedish population-based study even showed that generic statins demonstrated a better level of adherence

Table 6. Change from baseline to month 2 in liver function tests, serum creatinine and serum creatine kinase.

Characteristic	Statistic	Value at baseline	Value at month 2	Change between baseline and month 2	*P* value
AST (µkat/L)	n	297	281	277	.002
	Mean (SD)	0.45 (0.17)	0.47 (0.18)	0.02 (0.10)	
	Min – max	0.13 – 1.03	0.17 – 1.13	-0.32 – 0.50	
ALT (µkat/L)	n	297	276	272	<.001
	Mean (SD)	0.45 (0.19)	0.48 (0.23)	0.04 (0.15)	
	Min – max	0.13 – 1.23	0.15 – 2.49	-0.32 – 1.66	
Serum creatinine (µmol/L)	n	293	269	264	.035
	Mean (SD)	76.04 (17.68)	79.58 (35.37)	0.00 (26.53)	
	Min – max	44.21 – 203.37	44.21 – 636.62	-35.37 – 433.26	
Serum creatine kinase (µkat/L)	n	182	164	161	.002
	Mean (SD)	1.33 (0.66)	1.41 (0.71)	0.09 (0.38)	
	Min – max	0.2 – 3.52	0.3 – 3.47	-1.2 – 1.38	

and prescription refill than innovator statins.[27] Another study showed that the increased level of adherence when using generic statins reduced the rate of hospitalization for an acute coronary syndrome or stroke as well as all-cause mortality.[28]

On average, 82.5% of our patients achieved their LDL-C target and there was no difference between dose groups in terms of percentage of goal attainment. In the DISCOVERY trial, which compared the efficacy of atorvastatin to that of rosuvastatin, investigators reported that 83.4% of patients on the latter achieved their targets.[29] This high percentage was even reported in studies following patients switching from other statins to rosuvastatin.[30]

In our study, generic rosuvastatin reduced TGs by 13.2% and increased HDL-C by 8.2% after 8 weeks of treatment. A systematic review of 108 trials of rosuvastatin reported a 7.3% increase in HDL-C levels with rosuvastatin, which is comparable to our results. This review, however, reported a 19.7-26.7% reduction in TG levels for 10-40 mg/day of rosuvastatin use. This difference can be due to the relatively low baseline TG levels in our study compared to those usually reported in trials.[31]

In our study, generic rosuvastatin was well tolerated. The AEs reported during the 8 weeks of therapy were consistent with the literature. Earlier studies on the innovator showed similar AE types but higher AE rates than reported in our study.[22,29]

Although generic rosuvastatin therapy in our study produced a statistically significant elevation in the levels of serum aminotransferases, creatinine, and creatine kinase levels, all changes observed were not clinically significant since mean levels remained within the normal range. This is supported by several trials in which no clinically significant elevation of levels occurred. Even for slight increases, studies suggest that they were only initial changes and no further increases occurred over time.[22,32]

The limitations of the study include its observational nature and lack of a control group, and the relatively short duration of follow-up, which might limit the generalizability of our results. A broader population and longer period of observation might have further supported our results. However, RCTs also have their drawbacks. While several RCTs were done in the early stages before and after approval of rosuvastatin, the generalizability of these RCTs is also limited due to their strict inclusion/exclusion criteria. Thus, there is a need for studies designed like this one to simulate real-life non-research settings.

Rosuvastatin is commonly used in Lebanon. A previous cross-sectional study in Lebanese and Jordanian dyslipidemic patients reported that rosuvastatin was the third most used statin (21.2%) in these populations.[20] The same study, however, reported that LDL-C goals were not achieved in 67.2% of patients with very high cardiovascular risk. It is hoped that with the cost saving of using a generic form of this potent statin, the use of this agent will increase, helping a greater proportion of patients achieve their target LDL-C goals.

Although rosuvastatin is generally found to be effective in reducing the LDL-C, the cost of the drug might be of concern to many patients. In Lebanon, Superstat is 33% to 45% less expensive than the innovator drug at available doses. The LDL-C lowering profile of this rosuvastatin generic at a lower cost with no increased risk of AEs will be beneficial and affordable and will reduce health expenses, especially since long-term use is needed for both primary and secondary prevention of CAD. Conducting a cost-effectiveness study might further support this hypothesis.

In conclusion, this observational study showed that a generic rosuvastatin was efficacious and safe in treating hypercholesterolemia for the prevention of CVD in this pool of mostly high-risk Lebanese subjects. The drug showed a favorable safety profile and was able to significantly reduce LDL-C levels and to help in achieving LDL-C target levels in the majority of the patients after only two months of treatment.

Statement of conflict of interest

The generic formula, Superstat (Resova in Saudi Arabia) was not supplied by the manufacturer and sponsor, Hikma Pharmaceuticals. None of the authors or participating centers had any contractual agreement with the pharmaceutical company. The authors received investigator fees from the sponsor of this study but the company had no role in data collection, analysis, and interpretation, nor in the preparation of the manuscript. The sponsor contracted with an independent clinical research organization (CRO) (Clinserv international, Beirut, Lebanon) to conduct the study, collect and analyze the data, and prepare the manuscript on its behalf. The contractual agreement was between the sponsor and the CRO. The authors were not part of this agreement. Authors and investigators have signed the investigator protocol endorsement page in the study protocol. The signed principle investigator agreements were between the CRO and the authors directly.

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REFERENCES

1. WHO. The world health report 2002: reducing risks, promoting healthy life. World Health Organization; 2002.
2. López AD, Murray CJ. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Harvard School of Public of Public Health; 1996.
3. Hiatt WR, Smith RJ. Assessing the clinical benefits of lipid-disorder drugs. N Engl J Med. 2014;370(5):396-9.
4. Catapano AL, Reiner Z, De backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis. 2011;217(1):3-46.
5. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2011;42(1):227-76.
6. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288(23):2998-3007.
7. Toth PP. An update on the benefits and risks of rosuvastatin therapy. Postgrad Med. 2014;126(2):7-17.
8. Rahilly-tierney CR, Spiro A, Vokonas P, Gaziano JM. Relation between high-density lipoprotein cholesterol and survival to age 85 years in men (from the VA normative aging study). Am J Cardiol. 2011;107(8):1173-7.
9. Last AR, Ference JD, Falleroni J. Pharmacologic treatment of hyperlipidemia. Am Fam Physician. 2011;84(5):551-8.
10. Reiner Z, Catapano AL, De backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32(14):1769-818.
11. Pedersen TR, Kjekshus J, Berg K, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. Atheroscler Suppl. 2004;5(3):81-7.
12. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301-7.
13. Pedersen TR, Berg K, Cook TJ, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. Arch Intern Med. 1996;156(18):2085-92.
14. Olsson AG. Statin therapy and reductions in low-density lipoprotein cholesterol: initial clinical data on the potent new statin Rosuvastatin. Am J Cardiol. 2001;87(5A):33B-36B.
15. Paoletti R, Fahmy M, Mahla G, Mizan J, Southworth H. Rosuvastatin demonstrates greater reduction of LDL-C compared with pravastatin and simvastatin in hypercholesterolaemic patients: a randomized, double-blind study. J Cardiovasc Risk. 2001;8(6):383-90.
16. Olsson AG, Istad H, Luurila O, et al. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. Am Heart J. 2002;144(6):1044-51.
17. WHO. NCD country profiles - Lebanon 2011. World Health Organization; 2011.
18. Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2011;(1):CD004816.
19. Zhou Q, Liao JK. Statins and cardiovascular diseases: from cholesterol lowering to pleiotropy. Curr Pharm Des. 2009;15(5):467-78.
20. Azar ST, Hantash HA, Jambart S, et al. Factors influencing dyslipidemia in statin-treated patients in Lebanon and Jordan: results of the Dyslipidemia International Study. Vasc Health Risk Manag. 2014;10:225-35.
21. Tan AT, Low LP, Lim CH, Tan CE. Effects of rosuvastatin on low-density lipoprotein cholesterol and plasma lipids in Asian patients with hypercholesterolemia. J Atheroscler Thromb. 2009;16(4):509-16.
22. Olsson AG, Pears J, Mckellar J, Mizan J, Raza A. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. Am J Cardiol. 2001;88(5):504-8.
23. Schwartz GG, Bolognese MA, Tremblay BP, et al. Efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolemia and a high risk of coronary heart disease: a randomized, controlled trial. Am Heart J. 2004;148(1):e4.
24. Punithavathi N, Ong LM, Lena YL, Leekha S. A multicenter study in Malaysia to determine the efficacy and safety of a generic atorvastatin. Med J Malaysia. 2009;64(2):150-4.
25. Ong LM, Punithavathi N, Lena YL, Mahanim O, Leekha S. Long-term efficacy and safety of a generic atorvastatin in usual clinical care setting. Med J Malaysia. 2011;66(3):214-9.
26. Boh M, Opolski G, Poredos P, Ceska R, Jezovnik M. Therapeutic equivalence of the generic and the reference atorvastatin in patients with increased coronary risk. Int Angiol. 2011;30(4):366-74.
27. Trusell H, Sundell KA. Effects of generic substitution on refill adherence to statin therapy: a nationwide population-based study. BMC Health Serv Res. 2014;14:626.
28. Gagne JJ, Choudhry NK, Kesselheim AS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Ann Intern Med. 2014;161(6):400-7.
29. Strandberg TE, Feely J, Sigurdsson EL. Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study. Clin Ther. 2004;26(11):1821-33.
30. Schuster H, Barter PJ, Stender S, et al. Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. Am Heart J. 2004;147(4):705-13.
31. Adams SP, Sekhon SS, Wright JM. Lipid-lowering efficacy of rosuvastatin. Cochrane Database Syst Rev. 2014;(11):CD010254.
32. Brewer HB. Benefit-risk assessment of Rosuvastatin 10 to 40 milligrams. Am J Cardiol. 2003;92(4B):23K-29K.